Cover Photo From: Orbital Kaposi Sarcoma in an Adult Filipino Male: A Case Report by Keshia Lourdes Duyongco, Gary John Mercado, Maria Katherine Villanueva and Agustina Abelardo (see page 12).
THE MEDICAL CITY JOURNAL

The Medical City Journal is the official, peer-reviewed, open-access research publication of The Medical City under the supervision and management of the Clinical and Translational Research Institute (CTRI). TMC Journal caters to all research of the The Medical City network including, but not limited to the following: clinical and biomedical research, case reports, hospital quality improvement research, hospital guidelines/ policy research, novel protocols, systematic literature review and meta-analysis. The aim of TMC Journal is to facilitate dissemination of clinically relevant information to other health practitioners and to the general public.

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MESSAGE FROM THE EDITOR-IN-CHIEF

Dear Readers –

It is with great pleasure that I (finally!) present to you the very first issue of The Medical City Journal.

For this First Issue, we decided to highlight original research led by TMC residents, staff, and employees from all different disciplines. The topics are varied, ranging from original articles looking at novel use of i-Phone for diabetic retinopathy, a review of the adverse effects of steroids on pre-term infants, and a second look at coconut oil. The case reports also highlight a spectrum of different diseases. All are clinically relevant and interesting, regardless of specialization.

This journal is in its infancy. Indeed, the road has been long and bumpy, and the learning curve steep. But a journey on the road less traveled by is worth it, and I hope you support this endeavor by reading the articles in this issue, and contributing future works (http://ctri.themedicalcity.com/).

Our hope is to eventually establish this journal as a platform for publishing high quality health-related research showcasing the talents of TMC.

Certainly, this issue would have been impossible to publish without the hardwork of the Clinical and Translational Research Institute, its proficient worker Mark B. Carascal, who has been tireless in pursuit of this project, and all of our submitting authors, who have labored in the production of their manuscripts, and have chosen TMC Journal as the journal they would like to publish in.

Enjoy,

C.L. Abad
March 2018
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Original Article

Dilated Smartphone Imaging for the Detection and Grading of Diabetic Retinopathy

Keshia Lourdes L. Duyongco,1* Milagros H. Arroyo,1 Victor Jose L. Caparas,1 Paolo Antonio S. Silva1,2
1Department of Ophthalmology, The Medical City, Ortigas Avenue, Pasig City, Philippines; 2Joslin Diabetes Center, Boston, Harvard Medical School, Massachusetts, USA
*Contact Details: keshiaduyongcomd@gmail.com

ABSTRACT: The recent interest in the efficacy of smartphones for fundus imaging to screen for diabetic retinopathy (DR) warrants further research due to its accessibility, portability, connectivity, and relatively low cost. This study aims to determine the diagnostic efficacy of dilated smartphone fundus imaging for the detection and grading of diabetic retinopathy. This is a single institution, hospital-based, prospective diagnostic validation study. Twenty-eight adult patients with diabetes (55 eyes) underwent dilated fundus imaging through two modalities: (1) iPhone 6s (Apple, Inc., Cupertino, California, USA) and (2) ultrawide field Optos fundus camera. An independent trained retina specialist graded both iPhone and Optos images for DR and diabetic macular edema (DME). A second retina specialist adjudicated grading discrepancies. Agreement between smartphone and 100-degree Optos image grading for DR was good to excellent (kappa= 0.79, 95% confidence interval [CI], 0.67-0.92; weighted kappa= 0.90, 95% CI, 0.85-0.96). Compared to 100-degree Optos fundus imaging, the sensitivity and specificity of dilated smartphone fundus imaging for the detection of referable DR, defined as at least moderate nonproliferative DR and/or DME, were 93.6% (95% CI, 78.6-99.2) and 100% (95% CI, 85.1-100), respectively. All of the patients who underwent dilated smartphone fundus imaging experienced no discomfort or untoward adverse events. In summary, dilated smartphone fundus imaging is a highly specific and sensitive tool for the detection of patients with DR. Given the inherent capability of the smartphone to transmit images, this technique is a promising and effective means for eye care professionals in remote and/or resource-poor areas to screen and monitor patients with DR with guidance from retina subspecialists from afar.

Keywords: detection; diabetic retinopathy; screening; smartphone; telemedicine

INTRODUCTION

Diabetic retinopathy remains a leading cause of blindness and decreased quality of life in both developed and developing countries. Early detection and treatment of diabetic retinopathy can prevent severe vision loss. Unfortunately, the recognition, monitoring, and treatment of diabetic retinopathy in resource poor settings remains to be a challenge due to the limited number of specialists, high cost of screening equipment, and poor access to eye care. Given this, remotely interpreted fundus imaging, also described as telemedicine, has emerged as a cost-effective screening method for diabetic retinopathy.

The current standards of care for diabetes require that a dilated eye examination be performed by an ophthalmologist within five years of diagnosis for type 1 diabetes, and at the time of diagnosis for type 2 diabetes. This should be followed by regular annual or semi-annual eye examinations, based on the evidence of retinopathy. In areas where access to ophthalmologists or retina subspecialists is limited, fundus photography with remote reading by a trained eye care provider is an acceptable means of screening for diabetic retinopathy. Clinical examinations are necessary when the fundus photos are ungradable or when retinal abnormalities are detected.

Unfortunately, utilization of eye care services remains low, particularly in poor and far-flung communities where access to health care is problematic. The utility of smartphones for capturing fundus images to screen for diabetic retinopathy has been suggested but its efficacy remains undocumented. In contrast to standard fundus cameras, the major advantages of smartphone fundus imaging include accessibility, portability, connectivity, and relatively low cost. Because of its possible application in areas with limited access to retina specialists and fundus cameras, studies on this technique in the context of telemedicine are relevant. In the Philippines, the potential use of this technology has yet to be explored. This study aimed to determine the diagnostic efficacy of dilated smartphone fundus imaging for the detection and grading of diabetic retinopathy compared to the standard of care and describe patient experiences during dilated smartphone fundus imaging.

METHODOLOGY

Population and Sample

Twenty-eight patients were consecutively recruited from the outpatient clinic of the Department of Ophthalmology at The Medical City in Ortigas Avenue, Pasig City from August 15, 2017 to September 15, 2017. The sample size was computed based on the target kappa value of 0.80 and assumed baseline kappa value of 0.50 with alpha of 5% and power of 80%. Patients were eligible for the study if the following inclusion criteria were met: (1) age of at least 18...
years old and able to give informed consent, (2) diagnosed clinically with diabetes mellitus, defined as currently taking anti-diabetic medications or laboratory evidence of elevated fasting blood sugar (FBS) or glycated hemoglobin (HbA1c), and (3) willingness to undergo dilated fundus photography using iPhone 6s and Optos fundus camera. Exclusion criteria included: (1) any external adnexal pathology and overt media opacity, such as corneal opacities and dense cataracts that may obscure fundus images, (2) contraindication to pupil dilation: elevated intraocular pressure (IOP), defined as >21 millimeters of mercury by Goldmann applanation tonometry or anterior chamber angle narrowing by gonioscopy, (3) unstable vital signs, defined as systolic blood pressure >140 millimeters of mercury and pulse rate >100 or <60 beats per minute, (4) history or evidence of hypersensitivity to tropicamide 0.5% and phenylephrine 0.5% eye drops for dilation, and (5) history or evidence of hypersensitivity to proparacaine hydrochloride 0.5% eye drops for topical anesthesia. Patient eligibility was determined through a review of each prospective study subject’s medical record at the time of that patient’s routine visit at the eye clinic. This study was approved by the Institutional Review Board of The Medical City, Pasig City.

Methods
Study Setting
The study was conducted after each patient’s eye examination, which included a dilated fundus exam, at the outpatient clinic.

Clinical Assessments
The following study procedures were performed during a single visit: (1) smartphone fundus imaging, (2) ultrawide field fundus imaging, and (3) survey on patient comfort during dilated smartphone fundus imaging. Prior to the study procedures, a member of the study team obtained the written informed consent. Baseline characteristics, which included demographics, medical and ocular history, were gathered from the outpatient record of the patient.

Smartphone Imaging
The principal investigator performed dilated smartphone fundus imaging using an iPhone 6s (Apple, Inc., Cupertino, California, USA) and a 20 diopter lens (Volk Optical, Mentor, OS). Each patient was asked to sit on a couch in a dark room at the Eye Center. Proparacaine hydrochloride 0.5% eyedrops were administered to the patient’s eyes as topical anesthesia. A member of the study team manually retracted the patient’s eyelids to expose the cornea during the procedure. The iPhone 6s was set on video mode with default settings at 1080 pixels and 30 frames per second. The camera’s flashlight was turned on and served as the coaxial light source. The 20 diopter lens was held 8 to 10 centimeters in front of the patient’s eye by the examiner’s thumb and index finger in one hand. The middle, ring, and little fingers were used to stabilize the hand and the lens on the patient’s brow.

Continuous videos of five fields of the retina: nasal, superior, temporal, inferior and posterior pole were recorded. To achieve this, the patient was instructed to look at a distant target in the direction of the area being examined (e.g., right eye: nasal – look left, superior – look upward, temporal – look right, inferior – look downward, posterior pole – look straight ahead).

The camera was held 10 to 35 centimeters from the lens along the patient’s pupillary axis. The 20 diopter lens was placed close enough to the patient’s eye to ensure that the pupil was centered on the screen. Once properly centered, the lens was moved further away from the corneal surface until the retina could be viewed. It is important for the patient’s eye, lens and smartphone to be on the same axis in order to minimize light reflections and aberrations.

The principal investigator reviewed all recorded videos. A screen shot of the best representative image was captured for all five fields (Fig 1A). Using the Adobe Photoshop Express (Adobe Systems, United States) application for iPhone, the screen shot was inverted and cropped. A black border was also placed on each image (Fig 1B). All images were exported to Google Drive and subsequently downloaded to the computers in The Medical City Eye Center Reading Room.

Patient Comfort Survey
Patients were asked to assess their level of comfort during dilated smartphone fundus imaging by a member of the study team. The following scale adapted from a user feasibility study was used to answer the following question: “How comfortable were you during fundus imaging using the smartphone?”: 1 – Very uncomfortable, 2 – Somewhat uncomfortable, 3 – Neutral, 4 – Somewhat comfortable, 5 – Very comfortable.

Ultrawide field imaging
Ultrawide field fundus imaging was performed by a trained ophthalmic technician using the Optos fundus camera (Dunfermline, Scotland, United Kingdom). Images were reacquired until the best image quality was obtained. All Optos images were masked in the periphery to produce 100-degree views of the retina based on Early Treatment Diabetic Retinopathy Study (ETDRS) standards (Fig 2). These served as the gold standard for grading diabetic retinopathy and diabetic macular edema.

Image Grading Protocol
Fundus images from the smartphone and from the Optos camera were coded using an identification number and randomly graded by a masked independent retina reader (R.P.S.) for the presence and severity of diabetic retinopathy and diabetic macular edema. The smartphone images were graded prior to the 100-degree Optos images.
The following scale based on the ETDRS was used for grading DR severity: No retinopathy, Mild non proliferative diabetic retinopathy (NPDR), Moderate NPDR, Severe NPDR, Proliferative diabetic retinopathy (PDR), High Risk PDR, and Ungradable. Diabetic macular edema (DME) was graded as: No DME, DME, Clinically significant macular edema (CSME), and Ungradable.

All images were reviewed at The Medical City Eye Center reading room through a 27-inch wide screen monitor (Asus; Asustek Computer Inc, Taiwan) with 1920 x 1080 resolution. Microsoft Office 2010 Picture Manager was used to adjust the contrast, brightness, and midtone of each image by the retina reader as needed. Disagreements regarding DR severity between smartphone and 100-degree Optos images were adjudicated by a second masked retina reader (P.S.S.). The adjudicated image grading for DR and DME were used in the data analysis.

Analysis

The agreement of DR and DME grading of images obtained via smartphone versus images obtained via Optos ultrawidefield camera was assessed using the kappa statistic (simple and linear weighted). Interpretation of kappa values was based on Landis and Koch (0.0 to 0.2 = slight agreement; 0.21 to 0.40 = fair agreement; 0.41 to 0.60 = moderate agreement; 0.61 to 0.80 = substantial agreement; and 0.81 to 1.00 = almost perfect agreement). In addition, the sensitivity, specificity, positive predictive value, and negative predictive value of dilated smartphone fundus imaging for the detection of referable and vision-threatening diabetic retinopathy were calculated assuming that the 100-degree Optos images provided the true diagnosis. The 95% confidence intervals were also computed.

Referable DR was defined as: at least moderate NPDR and/or DME. Vision-threatening diabetic retinopathy (VTDR) was defined as: at least severe NPDR and/or CSME. Statistical analyses were performed using SAS software version 9.2 (SAS, Inc, Carey, North Carolina, USA).

RESULTS

A total of 28 patients (55 eyes) completed the study [the 56th eye was excluded due to a media opacity (dense cataract) that obscured the fundus (exclusion criteria)]. Baseline characteristics of patients are reported in Table 1. The mean age (+ standard deviation) was 59.5 ± 10 years. Twenty-three (82.1%) patients were female. The mean duration of diabetes was 9.6 ± 7.3 years. Of the 55 eyes, 40 eyes (72.7%) had a best-corrected visual acuity greater or equal to 20/40 but less than 20/20. Thirty-seven (67.3%) were phakic and 18 eyes were pseudophakic (32.7%).

Based on 100-degree ETDRS Optos imaging, 47 eyes had DR (85.1%), 8 eyes had DME (14.5%) and 12 eyes had CSME (21.8%).
Table 1. Baseline Demographics, Medical and Ocular Characteristics

<table>
<thead>
<tr>
<th>Demographics (n = 28 patients)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (^a)</td>
<td>59.5 ± 10 (34 to 85)</td>
</tr>
<tr>
<td>Gender (^b)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>23 (82.1%)</td>
</tr>
<tr>
<td>Male</td>
<td>5 (17.9%)</td>
</tr>
<tr>
<td>Medical characteristics</td>
<td></td>
</tr>
<tr>
<td>(n = 28 patients)</td>
<td></td>
</tr>
<tr>
<td>DM duration (years) (^a)</td>
<td>9.6 ± 7.3 (0.6 to 25)</td>
</tr>
<tr>
<td>Ocular characteristics</td>
<td></td>
</tr>
<tr>
<td>(n = 55 eyes)</td>
<td></td>
</tr>
<tr>
<td>ETDRS visual acuity (^b)</td>
<td></td>
</tr>
<tr>
<td>≥ 20/20</td>
<td>9 (16.4%)</td>
</tr>
<tr>
<td>&lt;20/20 to ≥ 20/40</td>
<td>40 (72.7%)</td>
</tr>
<tr>
<td>&lt;20/40 to ≥ 20/100</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>&lt;20/100</td>
<td>5 (9.1%)</td>
</tr>
<tr>
<td>Lens (^b)</td>
<td></td>
</tr>
<tr>
<td>Phakic</td>
<td>37 (67.3%)</td>
</tr>
<tr>
<td>Pseudophakic</td>
<td>18 (32.7%)</td>
</tr>
<tr>
<td>Retinopathy severity (^b,c)</td>
<td></td>
</tr>
<tr>
<td>No DR</td>
<td>7 (12.7%)</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>17 (30.9%)</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>8 (14.5%)</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>7 (12.7%)</td>
</tr>
<tr>
<td>PDR</td>
<td>11 (20.0%)</td>
</tr>
<tr>
<td>High risk PDR</td>
<td>4 (7.3%)</td>
</tr>
<tr>
<td>Ungradable for DR</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Total with DR</td>
<td>47 (85.1%)</td>
</tr>
<tr>
<td>Macular edema severity (^b,c)</td>
<td></td>
</tr>
<tr>
<td>No DME</td>
<td>30 (54.5%)</td>
</tr>
<tr>
<td>DME</td>
<td>8 (14.5%)</td>
</tr>
<tr>
<td>CSME</td>
<td>12 (21.8%)</td>
</tr>
<tr>
<td>Ungradable for DME</td>
<td>5 (9.1%)</td>
</tr>
</tbody>
</table>

DM – diabetes mellitus; DR – diabetic retinopathy; NPDR – nonproliferative diabetic retinopathy; PDR – proliferative diabetic retinopathy; DME – diabetic macular edema; CSME – clinically significant macular edema

\(^a\) Data presented as mean ± standard deviation (range)

\(^b\) Data presented as number (%)

\(^c\) Grading based on 100 degree ETDRS Optos photographs as gold standard (n = 55 eyes)

Diabetic retinopathy detection by the two imaging modalities: smartphone and 100-degree Optos fundus camera is presented in Table 2. Out of the 55 eyes, only 1 eye (1.8%) was ungradable by both 100-degree Optos imaging and by smartphone imaging due to media opacity. Among 54 gradable eyes for DR, exact agreement of DR severity between 100-degree Optos images and smartphone images was seen in 46 eyes (84%) with a simple \(\kappa\) of 0.79 (95% CI, 0.67 to 0.92) and weighted \(\kappa\) of 0.90 (95% CI, 0.85 to 0.96).

A total of 21 eyes (38.2%) did not have an exact match in the level of DR after evaluation of smartphone and 100-degree Optos images. After independent adjudications of smartphone and 100-degree Optos images, discrepancies in the DR level remained in 9 eyes (16.4%). The source of the discrepancies was found to be the missed detection of a single lesion-type in all 9 eyes. These lesions were hemorrhages/ microaneurysms (HMA) in 4 eyes, intraretinal microvascular abnormality (IRMA) in 3 eyes, and new vessels on the disc (NVD) in 2 eyes. Discrepancies in lesion detection were attributed to poor image quality by smartphone in 8 eyes and in Optos in 1 eye.

Diabetic macular edema detection by the two imaging modalities is presented in Table 3. Out of the 55 eyes, 5 eyes (1.8%) were ungradable by 100-degree Optos imaging due to media opacities obscuring the macula. Two of the 5 eyes were graded with no DME by smartphone. Among 50 gradable eyes for DR, exact agreement of DR severity between 100-degree Optos images and smartphone images was seen in 40 eyes (80%) with a simple \(\kappa\) of 0.63 (95% CI, 0.44 to 0.82) and weighted \(\kappa\) of 0.64 (95% CI, 0.44 to 0.85).

Data for sensitivity, specificity, and predictive values for referable diabetic retinopathy and vision-threatening diabetic retinopathy are presented in Table 4 and Table 5, respectively. Compared to 100-degree Optos fundus imaging, the sensitivity and specificity of diluted smartphone fundus imaging for the detection of referable DR were 93.6% (95% CI, 78.6-99.2) and 100% (95% CI, 85.1-100), respectively. The positive predictive value and negative predictive value of diluted smartphone fundus imaging for the detection of referable DR were 100% (95% CI, 88.1-100) and 92% (95% CI, 74.0-99.0), respectively. On the other hand, the sensitivity and specificity of diluted smartphone fundus imaging for the detection of VTDR were 92.0% (95% CI, 74.0-99.0) and 96.6% (95% CI, 82.2-99.9), respectively. The positive predictive value and negative predictive value of diluted smartphone fundus imaging for the detection of VTDR were 95.8% (95% CI, 78.9-99.9) and 93.3% (95% CI, 77.9-99.2), respectively.

As presented in Table 6, all 28 patients felt comfortable during dilated smartphone imaging with 13 patients (46.4%) rating their experience as “somewhat comfortable” and 15 patients (53.6%) rating their experience as “very comfortable”.

**DISCUSSION**

Few studies have compared smartphone fundus imaging to standard imaging equipment.\(^8\) This study is the first to compare dilated smartphone imaging using an iPhone 6s to an ultrawide field imaging fundus camera. The fundus images obtained with the smartphone had a high rate of accuracy for grading DR severity. Agreement between smartphone and 100-degree Optos image grading was good to excellent for DR, and good for DME. The smartphone was also sensitive and specific for detecting referable DR and vision-threatening DR. One reason for the higher agreement, sensitivity and specificity of smartphone images in this study as compared to previous studies may be the imaging of five fields: nasal, superior, temporal, inferior and posterior pole.\(^8\) The average number of images reviewed per study eye was 13 (minimum: 7, maximum: 21).
This allowed the acquisition of a larger field of the retina giving more information to the grader.

Several techniques for smartphone imaging have been reported and differ according to use of adapters and applications. A study reported the sensitivity and specificity of dilated smartphone imaging with an iPhone 5 using the Filmic Pro application to be 50% and 94%, respectively, compared to dilated fundus imaging. Another study compared dilated smartphone imaging of a single field with an iPhone 5s and the Paxos Scope adapter to clinical grading and demonstrated a sensitivity and specificity of 91% and 99%, respectively. In our paper, the authors preferred to perform smartphone imaging using the default settings of the iPhone with no additional adapters as demonstrated in previous techniques.

Table 2. Cross-Tabulation of Level of Diabetic Retinopathy in 100-degree ETDRS Optos Imaging and Smartphone Imaging

<table>
<thead>
<tr>
<th>DR Grading</th>
<th>No DR</th>
<th>Mild NPDR</th>
<th>Moderate NPDR</th>
<th>Severe NPDR</th>
<th>PDR</th>
<th>High Risk PDR</th>
<th>Ungradable</th>
<th>Total for Smartphone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No DR</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>16.4</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>1</td>
<td>14</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>29.1</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>16.4</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>10.9</td>
</tr>
<tr>
<td>PDR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>1</td>
<td>11</td>
<td>20.0</td>
</tr>
<tr>
<td>High Risk PDR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>5.5</td>
</tr>
<tr>
<td>Ungradable</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>Total for Optos (%)</td>
<td>7</td>
<td>17</td>
<td>8</td>
<td>7</td>
<td>11</td>
<td>4</td>
<td>1</td>
<td>55 (100)</td>
</tr>
</tbody>
</table>

DR – diabetic retinopathy; NPDR – nonproliferative diabetic retinopathy; PDR – proliferative diabetic retinopathy
κ statistic for agreement did not include images that were ungradable for diabetic retinopathy by 100-degree Optos imaging (n=1)
Simple κ statistic, 0.79 (95% confidence interval, 0.67 to 0.92)
Weighted κ statistic (linear), 0.90 (95% confidence interval, 0.85 to 0.96)

Table 3. Cross-Tabulation of Level of Diabetic Macular Edema in 100-degree ETDRS Optos Imaging and Smartphone Imaging

<table>
<thead>
<tr>
<th>DME Grading</th>
<th>No DME</th>
<th>DME</th>
<th>CSME</th>
<th>Ungradable</th>
<th>Total for Smartphone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No DME</td>
<td>27</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>33 (60.0)</td>
</tr>
<tr>
<td>DME</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3 (5.5)</td>
</tr>
<tr>
<td>CSME</td>
<td>3</td>
<td>3</td>
<td>10</td>
<td>0</td>
<td>16 (29.1)</td>
</tr>
<tr>
<td>Ungradable</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>3 (5.5)</td>
</tr>
<tr>
<td>Total for Optos (%)</td>
<td>30</td>
<td>8</td>
<td>12</td>
<td>5</td>
<td>55 (100)</td>
</tr>
</tbody>
</table>

DME – diabetic macular edema; CSME – clinically significant macular edema
κ statistic for agreement did not include images that were ungradable for diabetic macular edema by 100-degree Optos imaging (n=5)
Simple κ statistic, 0.63 (95% confidence interval, 0.44 to 0.82)
Weighted κ statistic, 0.64 (95% confidence interval, 0.44 to 0.85)
This study also shows that smartphone imaging was a relatively comfortable procedure, similar to the results of another study. In addition, the average time it took to complete the imaging of five fields per eye was 1 to 2 minutes which is comparable to previous studies.

The study has some limitations. First, a resident ophthalmologist with training in indirect ophthalmoscopy performed the smartphone imaging, and the same quality of images and therefore reproducibility of study results may not be achieved by non-ophthalmologists. Second, this study utilized a non-standard image output from a fundus camera as the gold standard. That is, the ultrawide field image that originally shows 200 degrees of the fundus was artificially masked to show 100 degrees based on ETDRS standards. Another study that compares the smartphone images to the unmasked 200-degree ultrawide field images may provide different results. Third, this study was performed in a tertiary hospital setting where patient demographics and disease characteristics may be different from a remote area.

Table 4. Sensitivity and Specificity of Smartphone Imaging for Referable Diabetic Retinopathy

<table>
<thead>
<tr>
<th>100-degree Optos Imaging</th>
<th>Not Referable DR</th>
<th>Referable DR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total (%)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smartphone Imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Referable DR</td>
<td>23</td>
<td>2</td>
<td>25 (46.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Referable DR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>29</td>
<td>29 (53.7)</td>
<td>0.94 (0.79 to 0.99)</td>
<td>1.00 (0.85 to 1.00)</td>
<td>1.00</td>
<td>0.92</td>
</tr>
<tr>
<td>Total (%)</td>
<td>23 (42.6)</td>
<td>31 (57.4)</td>
<td>54 (100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DR – diabetic retinopathy; CI – confidence interval
Data excludes images that were ungradable for diabetic retinopathy by 100-degree Optos imaging (n=1)
<sup>a</sup> – Referable diabetic retinopathy defined as at least moderate nonproliferative diabetic retinopathy and/or diabetic macular edema

Table 5. Sensitivity and Specificity of Smartphone Imaging for Vision-threatening Diabetic Retinopathy

<table>
<thead>
<tr>
<th>100-degree Optos Imaging</th>
<th>Not VTDR</th>
<th>VTDR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total (%)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smartphone Imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not VTDR</td>
<td>28</td>
<td>2</td>
<td>30 (55.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTDR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>23</td>
<td>24 (44.4)</td>
<td>0.92 (0.74 to 0.99)</td>
<td>0.97 (0.82 to 1.00)</td>
<td>0.96</td>
<td>0.93</td>
</tr>
<tr>
<td>Total (%)</td>
<td>29 (53.7)</td>
<td>25 (46.3)</td>
<td>54 (100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VTDR – vision-threatening diabetic retinopathy; CI – confidence interval
Data excludes images that were ungradable for diabetic retinopathy by 100-degree Optos imaging (n=1)
<sup>a</sup> – Vision-threatening diabetic retinopathy defined as at least severe nonproliferative diabetic retinopathy and/or clinically significant macular edema

There are also inherent limitations to smartphone fundus imaging. For instance, the need for pharmacologic dilation may limit the application of smartphone fundus imaging to ophthalmologists. With mobile transmission of images and data, assuring patient confidentiality and privacy may be problematic and should also be addressed. The technique of smartphone fundus imaging is technically similar to indirect ophthalmoscopy and requires time, practice, and experience to acquire high quality images. Image quality in smartphone fundus imaging is also largely affected by several factors—pseudophakic eyes tend to result in decreased image quality due to a higher rate of reflections and aberrations. Since light intensity is not modifiable for the iPhone 6s video mode, images on the retina for pseudophakic eyes appear pale as compared to phakic eyes (Fig 3). Image quality from the smartphone is also dependent on the skill of the photographer. Consequently, an experienced photographer is preferable to standardize the technique in this study.

Nonetheless, given its relatively high sensitivity and specificity for detection of referable diabetic retinopathy and possible integration into a telemedicine platform, smartphone fundus imaging is a promising adjunct tool for
screening and monitoring in areas with limited access to standard fundus cameras. Considering the scarcity and disproportionate urban distribution of retina subspecialists in the Philippines, and given that smartphone imaging is cost-effective, relatively easy to learn, and accessible, a compelling argument can be made to incorporate this technique in the training of new ophthalmologists.

Table 6. Patient Comfort during Dilated Smartphone Imaging

<table>
<thead>
<tr>
<th>Level of Comfort</th>
<th>(n=28 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Uncomfortable</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Somewhat Uncomfortable</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Neutral</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Somewhat Comfortable</td>
<td>13 (46.4%)</td>
</tr>
<tr>
<td>Very Comfortable</td>
<td>15 (53.6%)</td>
</tr>
</tbody>
</table>

Figure 3. (A) Smartphone fundus image of a pseudophakic eye. Note the pale appearance of the retina compared to Optos 100-degree image of the same eye. (B) Optos 100-degree image of the same eye. A white circle encloses the area corresponding to the first image.

CONCLUSION
Dilated smartphone fundus imaging is a highly specific and sensitive tool for the detection of patients with DR. Given the inherent capability of the smartphone to transmit images, this technique is a promising and effective means for eye care professionals in remote and/or resource-poor areas to screen and monitor patients with DR with guidance from retina subspecialists from afar.

ACKNOWLEDGEMENT
The authors would like to acknowledge the significant contributions of Dr. Kaye Lani Rea B. Locaylocay, Dr. Corrina Elise C. Samaniego, Mr. Noel D. Cruz, Dr. Recivall P. Salongcay, Dr. Ricardo M. Papa and The Medical City Eye Center staff.

REFERENCES
Case Report

Unexpected Scurvy Presenting with Proptosis: A Case Report

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ABSTRACT: Scurvy is a state of dietary deficiency of ascorbic acid, or vitamin C as it is more commonly known. Since the discovery of the link between scurvy and vitamin C, it has become a rare condition. We present a 5 y.o. Filipino female with proptosis. An intraorbital neoplastic process was primarily entertained. Only after magnetic resonance imaging (MRI) revealed bilateral supraorbital subperiosteal hematoma formation was scurvy considered and empiric treatment of vitamin C supplementation started, yielding significant improvement. Given the multiple tools that we have in the information age, MRI plays a role in helping diagnose an easily treatable condition.

Keywords: hemorrhage, MRI, proptosis, scurvy

INTRODUCTION

Since the discovery of the link between scurvy and vitamin C deficiency, scurvy has become an uncommon condition in all age groups. Cases of scurvy may still be found in industrialized societies, frequently among the extreme ages of the population. The initial presenting features of scurvy are nonspecific, ranging from fatigue to musculoskeletal complaints. As scurvy progresses, patients present with lethargy, osteoporosis and impaired wound healing. Laboratory workup may also reveal nonspecific results such as anemia. Left untreated, scurvy may have fatal complications.

In the pediatric population, scurvy usually involves symmetric bone disease and a tendency to hemorrhage. Because of its rarity, other conditions are often considered before its diagnosis, and a high index of suspicion in the proper clinical setting is needed. In the absence of x-ray findings, features of hemorrhage as seen through magnetic resonance imaging (MRI) can lead to its diagnosis. This case highlights a rare case of scurvy, its unique manifestations and findings seen on MRI.

CASE REPORT

A 5 y.o. female presented with a 6-month history of severe constipation associated with bloody stools, loss of appetite and body malaise. Multiple outpatient consultations were unrevealing, and led to assessments of constipation and growing pains. The patient was managed symptomatically with temporary relief. Initial radiologic work-up revealed normal x-rays of the extremities and chest as well as an unremarkable ultrasound of the whole abdomen. In the interim, the patient gradually developed progressive weakness, fatigue, body and joint pains. Three hours prior to consultation, she complained of bilateral eye pain and eyeballs “popping out,” prompting a visit to the emergency room.

The patient’s birth, past medical, developmental and personal/social histories were unremarkable. The patient’s feeding history was noted to be completely deficient in fruits and vegetables, with note of vomiting when eating the latter. Pertinent physical examination of the patient revealed bilateral proptosis with tenderness, generalized abdominal pain, gum swelling and body weakness. Workup involved a complete blood count, urinalysis, chest and skull x-rays, all of which were normal. No other radiographs were done. At this point, the initial impression was that of retinoblastoma. A referral was made to the Ophthalmology service whose assessment was neuroblastoma. She was then referred to the pediatric Hematology/Oncology service for further management.

On the 1st day of admission, MRI studies of the chest, brain, orbits and whole abdomen with contrast enhancement were requested to evaluate for malignancy. The MRI studies of the chest and abdomen were normal. The cranial and orbital MRI examinations (Figures 1 to 3) revealed bilateral orbital subperiosteal foci with features suggestive of hematoma formation and its mass effects. Based on these findings, a range of differentials including trauma, metabolic disorders, hemorrhagic diatheses, vaso-occlusion, and abscess formation, were considered. The unremarkable MRI of the chest and abdomen, along with a normal complete blood count made leukemia or neuroblastoma less likely. There was no history of trauma. The patient had an unremarkable past medical history, ruling out hemorrhagic diatheses and vaso-occlusion. As the patient did not present with fever, an infection was excluded from the differential diagnoses.

A metabolic disorder was considered given the patient’s feeding history, and empiric treatment with vitamin C was initiated. The patient’s clinical picture progressively improved. On the 3rd day of admission, the patient’s pain decreased significantly. By the 6th day, the proptosis resolved completely.

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Figure 1. T1 weighted fat suppressed gadolinium-enhanced MRI sequences of the (A) axial and (B) coronal planes of the head and orbits showing rim enhancing spindle-shaped predominantly hypointense masses occupying the superior extraconal regions of both orbits.

Figure 2. T2 weighted MRI sequences of the sagittal planes of (A) right and (B) left eyes, and (C) axial and (D) coronal planes of the head and orbits show the predominantly hypointense masses occupying the superior extraconal regions of both orbits.

Figure 3. (A) Diffusion weighted imaging (DWI) with (B) apparent diffusion coefficient (ADC) maps and (C) susceptibility weighted imaging (SWI) MRI sequences showing restricted diffusion with loss of signal in SWI of the masses occupying the superior extraconal regions of both orbits.
DISCUSSION

Scurvy is one of the oldest diseases known to humanity, with evidence of its existence as early as 1500 BC. It is a metabolic disorder specific to a deficiency in ascorbic acid. Ascorbic acid is an essential nutrient needed in the synthesis of collagen. Deficiency leads to impaired wound healing as well as impaired skin, bone and connective tissue formation.

Classic signs and symptoms include asthenia, bleeding disorders and gum abnormalities. These symptoms, however, are uncommon and are seen in its later stages. Patients will usually have nonspecific signs and symptoms. Musculoskeletal symptoms such as arthralgia, myalgia and hemorrhage are present in up to 80% of cases of scurvy. Among children, lower extremity pain, limping and inability to walk are frequently encountered. Oral symptoms present as swelling, bleeding gums and loosening of teeth. Dermatologic manifestations include petechiae, ecchymoses, hyperkeratosis and perifollicular hemorrhage. Initially, our patient presented with severe constipation, loss of appetite and body malaise. Of these nonspecific signs and symptoms, our patient eventually developed musculoskeletal complaints, with oral findings of gum swelling only noted in the emergency room.

Scurvy in children presents with a wide spectrum of clinical manifestations. These include rashes and weakness, difficulty walking, musculoskeletal pain, and even bilateral proptosis. According to Agarwal et al, Vitamin C deficiency generally leads to symmetric bone disease and a tendency to hemorrhage. Of the two, the former frequently attracts the attention of parents and caregivers prompting medical consultation. In our patient, proptosis as a manifestation of intraorbital subperiosteal hemorrhage prompted the ER visit.

Diagnosis of scurvy is made through clinical manifestations of a scorbutic state, biochemical indices and supportive history of vitamin C deficiency. Serum ascorbic acid levels may be low to normal in the presence of scurvy. Recent Vitamin C supplementation, may lead to normal serum ascorbic acid levels in patients with scurvy. The best confirmation of the diagnosis of scurvy is its resolution following vitamin C administration. In the Philippines, testing for serum ascorbic acid is not available. For this patient, the diagnosis of scurvy was confirmed when the patient had drastic improvement upon empiric treatment with ascorbic acid.

Our patient presented with features of painful proptosis and nonspecific symptoms. Scurvy can mimic malignancy, especially leukemia. MRI findings in scurvy have been described to reflect the underlying pathophysiology of hemorrhage in the periosteum, which can be seen in the shafts of long bones. When seen along with periostitis, metaphyseal changes and heterogeneous bone marrow signal intensity, scurvy should be included in the differential diagnosis, but these were absent in our patient. MRI findings of scurvy in the orbits can present with hematoma formation as previously reported. The diffuse marrow changes expected of malignancy such as leukemia are typically absent.

Orbital subperiosteal hematoma is not pathognomonic for scurvy. It may be associated with a history of facial trauma or barotrauma as well as Valsalva maneuver, bleeding diathesis, anticoagulation therapy and other systemic diseases. Rupture of the diploic veins between the periosteum and the bony orbit, results in local hemorrhage with subsequent hematoma formation. Left untreated, this may spontaneously resolve or enlarge to cause proptosis.

Our patient presented with a 6-month history of severe constipation accompanied by crying episodes and bloody stools. Prolonged duration of recurrent Valsalva maneuver prompted by severe constipation can cause orbital hemorrhage owing to the increased vascular fragility caused by defective collagen formation in vessel basement membranes. We thus establish the connection between constipation, scurvy, orbital subperiosteal hematoma formation and proptosis. Ocular lesions are uncommon manifestations of scurvy and most present with subconjunctival or orbital hemorrhages with the latter typically located in the superior and subperiosteal areas. With bilateral extraorbital MRI findings suggestive of subperiosteal hematoma formation, and given the other features described above, scurvy was considered in our patient and empiric treatment with ascorbic acid was started. Our patient had dramatic improvement and resolution of symptoms, strongly reflecting the need to be aware of this easily missed deficiency.

CONCLUSION

Scurvy is a rare condition, is often associated with nonspecific symptoms, and can easily be missed. Obtaining a thorough history including dietary habits is imperative. Although scurvy often presents with radiographic findings of bone changes in the extremities, it can present with signs of hemorrhage in the orbits. MRI findings of extraorbital subperiosteal hematoma formation seen in the absence of other radiologic findings should prompt consideration of scurvy in the differential diagnosis.

ACKNOWLEDGEMENT

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REFERENCES


Case Report

Orbital Kaposi Sarcoma in an Adult Filipino Male: A Case Report

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ABSTRACT: A distinctive case of orbital Kaposi sarcoma is reported to: (a) describe the unique presentation of the tumor, (b) identify key histomorphologic and immunohistochemical characteristics, and (c) discuss the challenges and issues in management. A 33-year-old Filipino male presented with a 5-month history of progressive proptosis of the left eye with associated blurring of vision, diplopia, and discomfort in eye movement. Magnetic resonance imaging (MRI) showed an abnormally enhancing intracranial mass in the left retro-orbital area with mass effects. Excision biopsy revealed a low-grade vasoproliferative neoplasm with positive CD34 immunostaining consistent with Kaposi sarcoma. Serologic test for HIV was positive. HIV-associated Kaposi sarcoma can occur in unusual locations including the orbit and should be considered in young, high-risk individuals presenting with ocular complaints.

Keywords: AIDS, HIV, Kaposi sarcoma, orbit, proptosis

INTRODUCTION

Kaposi sarcoma (KS) is a vasoproliferative disease of endothelial origin. It has four epidemiologic variants: classic (sporadic or Mediterranean), endemic (African), iatrogenic (post-transplant), and epidemic (acquired immunodeficiency syndrome or AIDS-associated).1,2 KS is an AIDS-defining illness, and is considered to be the most frequently observed AIDS-associated malignancy worldwide.3 The advent of antiretroviral therapy in 1996 has led to a decline in the incidence of AIDS-associated KS. The HIV/AIDS Cancer Match Study reported an average yearly decline of 6% during 2000 to 2010 in the United States. Nonetheless, the risk of KS among HIV-positive individuals remains elevated 800-fold compared to the general population.3 There are no published data on the epidemiology of KS in the Philippines. We present a case of AIDS-associated KS with a distinctive clinical manifestation.

CASE REPORT

A 33-year old male admitted at The Medical City due to perianal abscess was referred to ophthalmology for proptosis of the left eye.

Five months prior to admission, the patient noted discomfort, blurring of vision, and slight proptosis of the left eye. He had palpitations and heat intolerance but denied tremors and weight loss. He was assessed to have Graves Disease and was started on methimazole with poor compliance. Three months prior to admission, progression of symptoms on the left eye prompted consult with an ophthalmologist. Thyroid eye disease was entertained at this time. Magnetic resonance imaging (MRI) of the orbits was requested, but the patient was lost to follow-up. Persistence of proptosis on the left eye with deterioration of vision, pain on eye movement, and diplopia prompted a subsequent ophthalmologic consult.

Review of systems was unremarkable. The patient had no history of trauma, eye surgeries, medications or spectacle use. Other medical conditions included untreated hepatitis B, bronchial asthma, and allergy to seafood and ibuprofen. There was family history of diabetes and hypertension.

The patient attained a college degree and worked as a call center agent. He was a previous smoker and occasional alcohol beverage drinker, and denied illicit drug use. He reported prior sexual relations with a male partner.

At the time of referral, vital signs were stable: blood pressure was 100-110/60-80 mmHg, heart rate 91 beats per minute, respiratory rate 20 cycles per minute, and temperature 37.5°C. Body mass index was normal at 18.7 kg/m². There was a 10 cm x 5 cm abscess palpable on the right perianal area. The rest of the physical examination was unremarkable.

Distance visual acuity was 20/25 corrected to 20/20 on the right eye and counting fingers at 1-foot on the left eye. Near visual acuity was J+ on the right eye and J16 on the left eye. Grossly, the left eye was propoited by 11mm and exotropic by 30 prism diopters via Hirschberg with minimal conjunctival hyperemia and clear discharge. The right eye was grossly unremarkable. The right pupil was 2-3 mm, round, and briskly reactive to light with no relative afferent defect. The left pupil was 3-4 mm, sluggishly reactive to light, with a relative afferent defect. There were limitations in the extraocular muscles of the left eye on all gazes (-2), which was worst on abduction (-3). Binocular diplopia and occasional discomfort on the left eye was noted in all positions of gaza. The cornea was clear, the anterior chamber was deep, and the lens was clear on both eyes. Fundus exam on the left eye through clear media showed a hyperemic disc with indistinct borders, a cup-to-disc ratio of 0.3, and choroidal folds. There were no retinal vasculature changes, hemorrhages, exudates, or chorioretinal scars. The fundus of the right eye was unremarkable.
Laboratory tests including a complete blood count, thyroid panel including thyroid-stimulating hormone (TSH), FT3, and FT4, sodium, potassium, creatinine, capillary blood glucose, chest x-ray, and 12-lead electrocardiogram were all within normal limits. The TSH receptor antibody was elevated at 3.26 U/L (normal values: 1.10-1.5 U/L), which is consistent with Graves disease.

MRI of the orbits revealed a left retro-orbital, intracanal mass measuring 3.0 cm x 2.4 cm x 3.3 cm (volume x width x anterior-posterior). The lesion was isointense to gray matter in T1-weighted image (Figure 1A) and predominantly hyperintense in T2-weighted image (Figure 1B). The mass displaced the left optic nerve medially. The left lateral rectus muscle was also compressed and appeared to be infiltrated by the lesion. The patient was advised to undergo orbitotomy with excision biopsy of the left retro-orbital mass.

![Figure 1](image_url) (A) T1-weighted and (B) T2-weighted MRI images of the orbit

Orbitotomy via transconjunctival approach with excision of the lesion and orbital exploration on the left eye was performed under general anesthesia. Intra-operatively, piecemeal excision of a pseudo-encapsulated mass measuring 2.75 cm x 2.75 cm was done. Microsections revealed spindle cells arranged in fascicles. The spindle cells formed slits, which contained extravasated red blood cells. Mitotic activity was low at 0-1/10 high power field. The individual tumor cells showed elongated, almost uniform nuclei with darkly colored and even chromatin, inconspicuous nucleoli, and tapered eosinophilic cytoplasm. Admixed with the tumor were lymphocytes and few eosinophils (Figure 2A, 2B). The histomorphologic features showed a round to spindle cell neoplasm, with mild nuclear pleomorphism, atypia and low mitotic count, suggesting a benign process. However, because of the cellularity, infiltrative nature, and geographic necrosis, a low-grade malignant neoplasm, possibly Kaposiform hemangioendothelioma was considered. Immunohistochemistry with CD3, CD20, CD21, CD1a, CD34, S-100 and Ki-67 was done. The tumor showed CD34 expression (Figure 3A) and a low Ki-67 expression (Figure 3B), which supports the diagnosis of a low-grade vasoformative neoplasm.

Two months after the surgery, the patient experienced headaches and had two episodes of generalized tonic-clonic seizures. A cranial MRI was done, which showed new multiple intracranial masses. HIV test was reactive. In the setting of HIV infection, the diagnosis of Kaposi sarcoma was made.

Four months after the surgery, the patient was admitted due to severe headaches accompanied by generalized body weakness, nausea, and vomiting. Near visual acuity on the left eye deteriorated to J16. The left pupil was dilated at 5 mm, non-reactive, with a relative afferent defect. Repeat cranial MRI demonstrated an “interval increase in the size of the enhancing left posterior temporal lobe intra-axial metastatic mass with development of intralesional micro hemorrhages and with slight progression of the perilesional edema, as well as interval increase in the sizes of the smaller nodules in the left cavernous sinus and right middle cranial fossa”.

DISCUSSION

The clinical behavior of AIDS-associated Kaposi sarcoma (KS) has evolved in terms of onset and organ involvement. AIDS-associated KS usually appears in the late stage of the disease, when there is significant immune dysregulation and low CD4 lymphocyte counts (<150 – 200 cells/mm³). However, recent studies have shown that KS can also occur as the initial manifestation of an HIV infection, particularly in young individuals aged between 20 to 50 years old.5,6
Figure 2: (A) Tumor cells are elongated with bland nuclei, inconspicuous nuclei, and tapered eosinophilic cytoplasm; High power view (40x, H&E stain). (B) Some areas show round tumor cells with ovoid nuclei, small nucleoli, irregular nuclear borders and variable eosinophilic cytoplasm; Extravasated red blood cells are seen in between tumor cells; High power view (40x, H&E stain)

Figure 3: (A) CD34- focally positive; CD34 is expressed in endothelial cells; It is also an indicator for vascular differentiation; CD34 expression is seen in 86% of Kaposi sarcoma. (B) Ki67- positive 20%; Ki67 highlights the proliferative portion of the cell cycle; Ki67 expression roughly correlates with tumor grade. (C) S100- negative; S100 is expressed in cells of neural origin. (D) CD3- negative; CD3 is a marker for T-cell derivation. (E) CD20- negative; CD20 is a marker for mature B-cell neoplasms. (F) CD21- negative; CD21 is a follicular dendritic cell marker. (G) CD1a- negative; CD1a is expressed in Langerhans cells and cortical thymocytes
AIDS-related KS tends to be multifocal or anatomically disseminated in contrast to the localized behavior of classic KS.\textsuperscript{7,8} It can occur in unusual locations such as the oral cavity, face, genital mucosa, lungs and gastrointestinal tract.\textsuperscript{5} In fact, one of the most common manifestations of AIDS is KS in the head and neck.\textsuperscript{8}

While ocular lesions usually arise in the ocular adnexa, specifically the eyelid, the lacrimal gland, and the conjunctiva, orbital involvement is an uncommon presentation.\textsuperscript{9} In 2000, a case of AIDS-associated KS manifesting as an anterior orbital mass was reported.\textsuperscript{10} Since then, our patient is the only documented case of AIDS-associated KS presenting similarly.

Table 1. Differential diagnoses characterized by histomorphologic and immunohistochemical features

<table>
<thead>
<tr>
<th>Differential Diagnoses</th>
<th>Histomorphologic Features</th>
<th>Immunohistochemical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi sarcoma</td>
<td>• Spindle cells forming slits containing red blood cells</td>
<td>• HHV-8 – positive nuclear expression</td>
</tr>
<tr>
<td></td>
<td>• Low mitotic activity</td>
<td>• CD31, CD34 - positive in blood vessels</td>
</tr>
<tr>
<td></td>
<td>• Mild nuclear pleomorphism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Admixed lymphocytes, hemosiderin-laden macrophages and other inflammatory</td>
<td></td>
</tr>
<tr>
<td>Kaposiform hemangioendothelioma</td>
<td>• Irregular vascular lobules that infiltrate soft tissue in a cannonball fashion</td>
<td>• CD31, CD34 - positive in capillary vessels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HHV-8 - negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• S100 - negative</td>
</tr>
<tr>
<td>Ancient schwannoma</td>
<td>• Truly encapsulated neoplasms and almost always solitary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cellular neoplasm composed of spindle cells often arranged in a palisading fashion or in an organoid arrangement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mitoses are usually absent or extremely scanty</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Blood vessels can be of such prominence as to simulate a vascular neoplasm</td>
<td></td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumor</td>
<td>• Extremely cellular spindle cell neoplasm</td>
<td>• S100 - positive</td>
</tr>
<tr>
<td></td>
<td>• Mitoses are usually abundant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Serpentine shape of the tumor cells arranged in palisades or whorls</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Epithelioid appearance of the endothelial cells of these vessels; presence of large gaping vascular spaces</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Geographic areas of necrosis, with tumor palisading at the edges</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Metaplastic tissues such as cartilage, bone, muscle, or blood vessels are present in approximately 15% of the cases</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>• Monoclonal lymphoid neoplasm composed of mononuclear Hodgkin cells and multinucleated Reed Sternberg cells</td>
<td>• CD3 – negative</td>
</tr>
<tr>
<td></td>
<td>• Variable mixture of inflammatory infiltrates such as lymphocytes and eosinophils</td>
<td>• CD20 – positive in 40% of cases</td>
</tr>
<tr>
<td>Langerhans cell histiocytosis</td>
<td>• Presence of Langerhans cells with indented and grooved nuclei, inconspicuous nucleoli and fine chromatin.</td>
<td>• CD21 – positive</td>
</tr>
<tr>
<td></td>
<td>• Background contains variable amounts of eosinophils, histiocytes, lymphocytes, and neutrophils.</td>
<td>• CD1a – positive</td>
</tr>
<tr>
<td></td>
<td>• Mitosis is variable</td>
<td></td>
</tr>
</tbody>
</table>

Due to its broad morphologic characteristics and similarities to several vasoproliferative lesions and spindle cell neoplasms, the histopathologic diagnosis of Kaposi sarcoma can be challenging.\textsuperscript{1,12} The differential diagnoses considered in this case were Kaposi sarcoma, Kaposiform hemangioendothelioma (KHE), ancient schwannoma, malignant peripheral nerve sheath tumor, Hodgkin’s lymphoma, and Langerhans cell histiocytosis. The likelihood of KS is exponentially increased in the setting of an HIV infection.\textsuperscript{8}

Tissue biopsy with immunohistochemistry is utilized in the diagnosis of Kaposi sarcoma.\textsuperscript{9,12} The histomorphologic features of KS include spindle cells forming slits containing red blood cells. The cells have mild nuclear pleomorphism, low mitotic activity and are admixed with lym-
phocytes, hemosiderin-laden macrophages, and other inflammatory cells. These findings are all present in the specimen obtained from our case.

CD34 expression and a low Ki-67 expression support the diagnosis of a low-grade vasoformative neoplasm. Kaposiform hemangioendothelioma shares almost the same histologic characteristics as KS, but it is seen almost exclusively in children. Immunostaining for HHV-8-latent nuclear antigen-1 (LNA-1) can differentiate KHE from KS, with KS being HHV-8-LNA-1 positive. This highly sensitive and specific test, however, is not available in the Philippines. Given that the patient is an adult male with HIV infection, the clinical, histologic, and immunologic features are more consistent with Kaposi sarcoma.

Immunohistochemistry also ruled out other disease entities. S100 expression was not observed, thereby removing ancient schwannoma and malignant peripheral nerve sheath tumor from the differentials (Figure 3C). The lymphoma markers (CD3, CD20 and CD21) were also negative, ruling out Hodgkin’s lymphoma (Figure 3D, 3E, 3F). Langerhans cell histiocytosis was also ruled out since CD1a was negative (Figure 3G). Table 1 contains the histomorphologic and immunohistochemical features of the disease entities considered in the case. Table 2 summarizes the immunohistochemical features of the differential diagnoses and the specimen obtained from the patient.

### CONCLUSION

Kaposi sarcoma is a low-grade vasoformative neoplasm with morphologic similarities to other vasoproliferative lesions and spindle cell neoplasms. This characteristic along with the atypical location and multifocal behavior of AIDS-associated KS can lead to challenges in diagnosis and management. In this case, determining the HIV status of the patient was essential in the diagnosis of KS given its unusual orbital presentation. HHV-8 LNA-1 staining can distinguish KS in patients with unknown HIV status; however, this test is currently not available in the Philippines. Therefore, Kaposi sarcoma should always be considered as a differential diagnosis in young, high-risk individuals presenting with ocular complaints.

Imaging also plays a role in the diagnosis of Kaposi sarcoma. With MRI, KS is seen as an abnormal enhancing tissue with low signal intensity on T1-weighted images and high signal intensity on turbo inversion recovery magnitude (TIRM) or T2-weighted images. This is consistent with the MRI findings of our case.

AIDS-associated KS tends to be a multifocal disease and therapy should be directed systemically. Chemotherapy and/or radiotherapy alone, despite having some palliative value, portends a poorer prognosis and less overall survival in AIDS-associated KS.

The use of highly active antiretroviral therapy (HAART) in AIDS-associated KS has been linked to disease regression 80% of the time and an increase in overall survival. The median time to response ranged from 3 to 9 months. KS flare, a phenomenon wherein there is a paradoxical worsening of KS while undergoing HAART, has also been described. HAART has decreased the incidence of KS among HIV patients in developed countries. Further research is still required to determine the impact of HAART on KS in developing countries.

Unfortunately, our patient was lost to follow-up before further work-up and treatment with HAART could be initiated.

### REFERENCES


Case Report

Defying Sutton’s Law: Primary Intrapulmonary Germ Cell Tumor: A Case Report

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ABSTRACT: Germ cell tumors are commonly found in the gonads. Intrapulmonary germ cell tumors are extremely rare and diagnosis requires exclusion of gonadal and extra-gonadal primary sites. Common signs and symptoms include chest pain, followed by hemoptysis and cough. Only a total of 67 cases of intrathoracic germ cell tumors have been published in the literature from 1939 to 2007. We report the case of a 23-year old Filipino male who initially presented with sore throat but on further diagnostic evaluation was found to have a pulmonary mass in the right lower lobe. Computed tomography imaging favored an infectious etiology but a more thorough evaluation with immunohistochemistry staining was consistent with a low grade intrapulmonary germ cell tumor. While Sutton’s law describes that it is reasonable to approach diseases with the most common conditions in mind, this case report highlights that exceptions do occur.

Keywords: computed tomography, germ cell tumor, intrapulmonary, Sutton’s law

INTRODUCTION

Sutton’s law states that in the practice of medicine, it is most prudent to look for disease conditions that are commonly encountered. A similar idea was coined by Dr. Theodore Woodward who stated that “When you hear hoof beats, think of horses not zebras”.

Approach to the diagnosis of a solitary pulmonary nodule or mass requires evaluation of the radiologic features that would facilitate its classification under either a benign or malignant process. Although there may be some overlap in their appearance radiographically, specific morphologic features are assessed to determine if a pulmonary focus has malignant potential. Particularly, features such as size, margins, contour, internal characteristics (i.e. attenuation, calcifications, wall thickness and air bronchogram), satellite nodules, halo sign and growth rate are evaluated.1

Discussed below is an unusual presentation of a germ cell tumor found in the intrathoracic area.

CASE REPORT

A 23-year old single male developed sore throat and fever lasting for about two weeks. He was given two different antibiotics with no relief of symptoms. The complete blood count was within normal limits. A chest radiograph was requested, which revealed a lung nodule in the right parahilar region (Figure 1). Our patient denied symptoms such as dyspnea, cough and weight loss. The patient had no co-morbidities or family history of malignancy. He was a non-smoker and an occasional alcoholic beverage drinker.

![Figure 1.](image1.png)

A contrast-enhanced chest CT scan was requested (Figure 2 and 3) which showed a well-defined soft tissue mass with smooth margins in the medial basal segment of the right lower lobe measuring 3.5 x 3.7 x 3.2 cm. No perilesional alveolo-interstitial opacities were detected. Moreover, the mediastinal compartments were intact with no demonstrable masses or enlarged lymph nodes. The primary consideration at this time was a tuberculous or granulomatous process. However, the possibility of a malignancy was not totally excluded. Tissue diagnosis and follow-up after empiric treatment was suggested.
Figure 2. Axial images (A) mediastinal and (B) lung windows showing a pulmonary mass in the medial basal segment of the right lower lobe.

Figure 3. Coronal (A) and sagittal (B) views showing the intrapulmonary location of the non-enhancing lung mass with soft tissue component.

The patient underwent CT-guided core needle tissue biopsy. Cytologic evaluation showed neoplastic cells occurring in clusters, some in acinar and rosette-like patterns with fairly uniform small round to ovoid nuclei, finely granular chromatin, inconspicuous nucleoli and ample eosinophilic cytoplasm (Figure 4). Immunohistochemistry was performed showing cells positive for the stains cytokeratin, TTF-1 and SALL 4. This profile was compatible with a germ cell tumor.

Open thoracotomy and right lower lung lobectomy was done yielding a 3.5 x 2 x 2 cm, well-defined encapsulated, cream white, soft and friable mass located in the medial basal segment.

A 0.5 cm hard subpleural nodule was also resected at the lateral aspect of the posterior basal segment. This showed chronic granulomatous inflammation on frozen section. Five resected hilar lymph nodes were negative for tumor infiltration.

Sonographic evaluation of the thyroid gland and testicles was done to search for a possible primary neoplasm, and revealed normal findings and a small left epididymal
head cyst, respectively. Metastatic work-up also included a computed tomography of the head, bone scan and sonographic evaluation of the whole abdomen. Workup only revealed cholelithiasis and bilateral non-obstructing nephrolithiases. No primary neoplastic focus was found elsewhere in the body.

The first case of intrapulmonary teratoma was documented by Mohr in 1939. Several studies postulated that intrathoracic teratomas originate from the thymic tissue of the third pharyngeal pouch. It is theorized that the primordial teratomatous focus in the potential mediastinum is caught up by the respiratory outgrowth; hence, it develops in the lung and not in the mediastinum.

Patients with intrapulmonary germ cell tumors commonly present with chest pain (52%), hemoptysis (42%) or cough (39%). The most specific symptom, if present, is trichoptysis (13%). None of these symptoms were present in our patient. Two-thirds of intrapulmonary germ cell tumors, particularly the teratoma type, occur in the upper lobes, usually in the left. There appears to be no documented case of germ cell tumors occurring in the lower lobes, as in our case.

Radiologically, an intrapulmonary teratoma usually presents as a lobulated mass, and may also show features of cavitation, consolidation or peripheral translucency. Particularly, computed tomography demonstrates discrete areas of different densities due to soft tissue, high focal fat content, punctate calcifications, or a combination of these features.

Intrapulmonary mature teratomas was defined in one study as lung masses with sizes ranging from 2.8 to 3 cm in diameter. They are usually cystic with loculations, while a sparse number of cases appear predominantly solid. Moreover, the cystic foci form connections with the bronchi and have an endobronchial component leading to the classic symptoms of hemoptysis and expectoration of hair or sebum. Interestingly, none of these features were in our patient: his CT imaging only showed a well-circumscribed soft tissue mass with smooth margins without any calcific, cystic or fat components.

Tissue histology is needed for definitive diagnosis. Tumors that may be present similarly include fetal type adenocarcinoma, germ cell tumor (immature teratoma alone or in combination with other germ cell tumors) and pulmonary bastoma. As such, the immunohistochemistry profile done in our patient played a crucial role in arriving at a more definitive diagnosis.
In outpatient, the SALL4 transcription factor was positive. This transcription factor is associated with embryonic pluripotency and is a useful immunohistoechemical marker of germ cell tumors. Another study involved the examination of 3215 tumors for SALL4 expression. Results showed that the transcription factor was consistently expressed in all germ cell tumors, except some trophoblastic tumors and mature components of teratomas.

In our patient, both TTF-1 and SALL4 transcription factors were positive. The TTF-1 strongly suggests the lung mass was a primary pulmonary neoplasm, while the SALL4 transcription factor confirms it as a germ cell tumor.

While the treatment of choice is surgical resection, germ cell tumors are very responsive to chemotherapy. However, since the intra-pulmonary location is extremely rare, no standardized treatment has been established. Published data discuss oncological management of mediastinal germ cell tumors, but no studies have been conducted showing that the same treatment regimen works effectively for the pulmonary intraparenchymal type. These tumors should be managed as a bronchopulmonary carcinoma.

CONCLUSION
Primary germ cell tumors of the lung parenchyma are extremely rare and only a few cases have been reported to date. While common imaging findings have already been established, this case highlights that germ cell tumors can present with atypical radiologic features. This may be attributed to the pluripotency of these types of tumors and as such, utmost care in diagnosis must be exercised when imaging findings do not conform to the typical presentation. Further evaluation with specific immunohistochemistry tests are often necessary and play a crucial role in correct diagnosis of these tumors.

REFERENCES
**Case Report**

Rash. What Lies Beneath.

A Case Report on Polyarteritis Nodosa in Pregnancy

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**ABSTRACT:** Polyarteritis nodosa is a rare form of vasculitis affecting single and medium arteries in about 2 to 3 persons in a million. The initial presentation is usually nonspecific, and due to the rarity of the condition is not always recognized. Rashes in pregnancy are often dismissed and the diagnosis of vasculitis is rarely considered. There is a need to systematically identify or rule out this rare condition as timely and appropriate interventions can significantly affect the pregnancy. We present a case of a 40-year-old multigravid diagnosed with polyarteritis nodosa who presented with progressive rashes on bilateral lower extremities during her 2nd trimester of pregnancy. We describe the history and physical examination findings of a pregnant patient with vasculitis and discuss the diagnostic approach to vasculitis in pregnancy.

**Keywords:** PAN, panniculitis, polyarteritis nodosa, rash, vasculitis

**INTRODUCTION**

Rash is a broad term for any change in appearance, color, or texture of the skin. Pregnancy, as a hormone-dependent state brings about a multitude of physiologic changes and exacerbates underlying pathologic disorders that bring out rashes. Vasculitis is the inflammation of systemic vasculature causing reactive damage to mural structures leading to loss of vessel integrity and compromise of the lumen resulting to downstream tissue ischemia and necrosis. Its effects may be self-limiting or catastrophic, depending on the vasculature affected, the initial manifestation may be nonspecific and as innocuous as a rash.

**CASE**

Patient is a 40-year-old Gravida 4 Para 3 (3-0-0-2), 34 1/7 weeks age of gestation, who came in for rashes on extremities. She had an unremarkable antenatal history, with regular prenatal check-ups. At 18 weeks age of gestation, approximately 4 months prior, patient noted gradual-onset of multiple painful macular erythematous lesions on bilateral lower extremities, concentrated around the ankle. There was easy bruisability with no other associated signs and symptoms. Persistence of symptoms prompted consult, and patient was advised observation.

At 28 weeks age of gestation, the patient noted progression of lesions, now affecting bilateral lower extremities, up to her thighs (Figure 1). She described severe joint pains on her ankles and knees affecting ambulation, which prompted consult. Upon physical examination, patient was noted to have multiple hyperpigmented nontender, movable nodules about 0.5 to 1 cm in diameter on bilateral lower extremities (Figure 2). There were no sensory or motor deficits and systemic exam was essentially unremarkable. Abdominal exam showed a nontender gravid abdomen with a fundic height of 30 cm, with good fetal heart tones and movement. At the time, patient denied any obstetric symptoms, no perceived uterine contractions, or watery or bloody vaginal discharge.

**Figure 1.** At 28 weeks age of gestation, erythematous, maculopapular lesions affecting bilateral lower extremities (up to the thighs)
The progressive development of the patient’s symptoms warranted further assessment and the patient was admitted for work-up and fetomaternal surveillance. Fetal monitoring with daily non-stress tests revealed reactive tracings with no uterine contractions. The biophysical profile score was 8/8 with no signs of intrauterine fetal growth restriction. Maternal doppler studies revealed findings suggestive of the development of maternal hypertension in the future, but no current fetal compromise. Betamethasone was given for fetal lung maturity in the event that expedient delivery was necessary.

Further work-up was then warranted to rule out an underlying systemic illness. Tumor markers were negative. Due to the cutaneous manifestations, the apparent lack of internal organ involvement, and the elevated ESR, the working impression was erythema nodosum. To confirm this, she was referred to Dermatology for a biopsy of a nodule on the left thigh. Patient was started on low-dose Prednisone which immediately resulted in improvement of pain and tenderness. Patient was sent home stable awaiting biopsy results, which later revealed medium sized polyarteritis nodosa. She was advised to continue Prednisone therapy with careful monitoring of symptoms. Perinatology planned to monitor the pregnancy via sonography and NST twice a week until delivery at term.

Further assessment of the patient’s rash revealed non-specific areas of erythema with multiple tender hyperpigmented nodules. Palpation revealed deep-seated nodules characteristic of an inflammatory process located beneath the dermis; hence a form of panniculitis was entertained. Despite a normal initial work-up, the patient’s symptoms progressed during the course of the admission. The nodules on bilateral lower extremities became tender to touch, with difficulty in ambulation due to the pain.

At 32 weeks age of gestation, multiple erythematous to hyper pigmented nontender, movable nodules about 0.5-1 cm in diameter on bilateral lower extremities

Given the patient’s presentation, she was referred to Hematology and Rheumatology services for co-management. Initial work-up was done revealing unremarkable liver and kidney function tests with normal bleeding parameters and no underlying coagulopathies.

Further assessment of the patient’s rash revealed non-specific areas of erythema with multiple tender hyperpigmented nodules. Palpation revealed deep-seated nodules characteristic of an inflammatory process located beneath the dermis; hence a form of panniculitis was entertained. Despite a normal initial work-up, the patient’s symptoms progressed during the course of the admission. The nodules

Figure 2. At 32 weeks age of gestation, multiple erythematous to hyper pigmented nontender, movable nodules about 0.5-1 cm in diameter on bilateral lower extremities

Figure 3. At 34 weeks age of gestation, active Condyloma Acuminata (arrows) along the cervical and vaginal canal

At 36 weeks age of gestation, patient was re-admitted for labor pains with gross blood in her urine. Internal exam revealed 1 cm dilatation of the cervical os, with note of erythematous papillary outgrowths on her cervix and vulvar areas aggregately measuring >2 cm (Figure 3). Further work-up was done to differentiate systemic vs cutaneous polyarteritis nodosa. Patient’s repeat urinalysis revealed microscopic hematuria despite little cervical change pointing to the possibility of renal involvement. In the background of preterm labor with at least 48 hours of steroid therapy for fetal lung maturity, the decision to expedite the delivery was made. Patient underwent primary cesarean
section with bilateral partial fimbriectomy and electrocautery of warts under spinal anesthesia. Post-operatively, patient tolerated the procedure well. She delivered a live pre-term, baby girl at 2853 grams, 36 weeks appropriate for gestational age with no signs and symptoms of vasculitis or cutaneous lesions. Post-operatively, the immunosuppressive therapy was continued with a decrease in number of cutaneous lesions and improvement of joint pains.

**DISCUSSION**

The patient presented with cutaneous lesions on the lower extremities. In a hormone driven state such as pregnancy, rashes are often manifestations of physiologic changes that come with pregnancy. The most common benign rash in pregnancy is pruritic urticarial papules and plaques of pregnancy (PUPP), which is managed conservatively. PUPP rash often manifests in the extremities but is always associated with abdominal involvement, which our patient did not have. Further assessment of the patient’s 6-week rash also revealed non-pruritic hyperpigmented tender nodules unlike the characteristic plaques and papules seen in PUPP. The characteristics of the lesions, the progressive course of the disease entity and the development of associated signs and symptoms such as arthralgia, joint pains, and gross hematuria were more consistent with a systemic disease, such as vasculitis.

**Vasculitis, especially in pregnancy, presents several diagnostic challenges. The clinical presentation often involves bilateral lesions on the lower extremities, which could be from an isolated cutaneous vasculitis or a clue to multisystem involvement. A rational approach is required in patients with suspected vasculitis.** An article published in the British Medical Journal suggests a systematic approach to the diagnosis of vasculitis by answering these 4 questions: Is this a condition that could mimic the presentation of vasculitis? Is there a secondary underlying cause? What is the extent of vasculitis? What specific type of vasculitis is this?

Several conditions such as infection, coagulopathies, and other inflammatory conditions such as Antiphospholipid Antibody Syndrome (APAS) mimic the presentation of vasculitis. The need to identify and rule out these disease entities is important as they warrant a different approach. Infections such as hepatitis B and C, are closely related to PAN and prognosis is significantly worse than non-HBV related PAN. Our patient’s hepatitis screening was unremarkable. Vasculitis is seldom the initial presenting manifestation in the setting of rheumatoid arthritis or systemic lupus erythematosus making these less likely. Drug exposure, a common secondary cause of vasculitis was not elicited in this patient.

After thoroughly ruling out other disease entities, there is a need to confirm the diagnosis polyarteritis nodosa (PAN), and assess its extent, as systemic involvement may call for more aggressive management. Confirmation of PAN is often done via biopsy of active lesions. In general, biopsy of a relatively new vasculitic lesion is most likely to show representative histologic changes. These include fibrinoid necrosis of a medium-sized muscular artery in the deep dermis with disruption of the internal elastic lamina, neutrophilic inflammation, and leukocytoclasis as seen in our patient (Figure. 4). Our patient’s work-up did not show systemic involvement and her PAN appeared limited to the cutaneous form. She responded well to Prednisone therapy and delivered a preterm baby girl via cesarean section with no complications. Post-operatively, the plan was to continue immunosuppressive therapy for 6 months to control symptoms.

Polyarteritis nodosa is a systemic necrotizing vasculitis that typically affects medium-sized muscular arteries, with occasional involvement of small muscular arteries. In the Philippines, data regarding PAN in pregnancy is very limited. As such, the specific effect of PAN in pregnancy and vice versa has only been studied in a small number of cases. It appears pregnancy does not have an effect on PAN nor does it cause progression. However, patients diagnosed with PAN late in pregnancy appear to have high maternal morbidity or mortality from complications of systemic involvement such as renal failure, gastrointestinal hemorrhage, and respiratory failure. Specific prognostic factors identified in surviving patients with PAN, followed up to 6 years, include heavy proteinuria, high serum creatinine, cardiomyopathy and gastrointestinal or neurological involvement. Our patient’s initial presentation was limited to cutaneous PAN but there was concern for possible progression to systemic PAN given her hematuria, which consequently led to the decision to expedite the delivery. There are case reports which have identified the development of cutaneous PAN in the fetus either at birth or neonatally. Our patient delivered a live preterm baby girl with no signs of cutaneous or systemic vasculitis, who was immediately roomed-in after delivery and sent home stable with her mother.
CONCLUSION
Polyarteritis nodosa in pregnancy is an underdiagnosed and under-reported phenomenon. Early recognition of a disease flare and differentiation from other disease entities in a pregnant patient can positively affect the pregnancy course and outcomes. A systemic diagnostic approach is necessary to allow for prompt identification and management of PAN. These patients are best cared for in a multidisciplinary setting, with access to specialized care. The cornerstone in the management of PAN during pregnancy is the use of corticosteroids. Its use has to be monitored thoroughly to avoid drug toxicity on both the mother and the growing fetus.

ACKNOWLEDGEMENT
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REFERENCES
Meta-Analysis

A Meta-Analysis on the long-term effects of repeated exposure to antenatal corticosteroids given to women at risk of preterm birth

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ABSTRACT: Randomized controlled trials have shown that repeated exposure to antenatal corticosteroids improve specific neonatal outcomes in infants born preterm but increases the risk of small for gestational age and low birth weight infants. Our study determined the effects of repeated exposure to antenatal corticosteroids on the development of cerebral palsy. A comprehensive search on PubMed, Science Direct, MEDLINE, Cochrane CENTRAL, HERDIN, and Google Scholar was done to identify randomized controlled trials, and three articles were included. The study population comprised of parturients between 24 1/7 to 34 6/7 weeks who were exposed to repeated doses of prenatal corticosteroids versus placebo. Our primary outcome was to determine the benefits of antenatal corticosteroids in reducing neonatal morbidities after preterm birth. Children exposed who experienced multiple treatments of antenatal corticosteroids had similar rates of developing cerebral palsy compared to those who were given a single course. Multiple doses of corticosteroid therapy given weekly or every 2 weeks did not provide an increased risk of developing cerebral palsy compared with a single course. However, long-term monitoring is necessary to determine its behavioral and cognitive effects during adolescence and adulthood.

Keywords: antenatal corticosteroids, preterm birth, preterm labor, repeat, rescue dose

INTRODUCTION

Preterm neonates are estimated to comprise 11.1% of all live births and preterm birth is a risk factor for at least 50% of all neonatal deaths.2 The Philippines ranks 8th out of 184 countries with preterm births and ranks 17th in total number of deaths caused by complications of prematurity. This increasing trend has been attributed to the increasing number of teenage pregnancies and lack of public awareness.3

Preterm delivery, regardless of the gestational age, causes short- and long-term neonatal morbidities including impaired neurodevelopmental functions, infection, learning impairment, visual disorders, and pulmonary complications.3 Since the pulmonary system is the last to develop, the lungs are the most commonly affected. Hence, prevention of preterm birth is the ultimate goal. One established intervention is the administration of antenatal corticosteroids to mothers at risk of preterm delivery. A randomized controlled trial on maternal administration of betamethasone showed a decreased incidence of respiratory distress syndrome in preterm infants from 15.6% to 10.0% as well as a reduction in neonatal mortality from 11.6% to 6.0%.1,2 Since then, the National Institutes of Health (NIH) along with American Congress of Obstetricians and Gynecologists (ACOG), has recommended the use of antenatal corticosteroids for women at risk of preterm birth between 24 and 34 weeks age of gestation.2 However, steroid effect diminishes through time and has raised concern in the management of women initially given a single course of steroids but still at risk of preterm delivery.

During the 1990’s, administration of repeated doses of antenatal corticosteroids became rampant triggering the National Institutes of Health (NIH) to caution on limiting the use of repeated corticosteroids to patients participating in randomized trials.

It has been standard practice in the Philippines to provide pregnant women between 24 to 34 weeks of gestation, at risk of preterm delivery, antenatal corticosteroids to enhance fetal lung maturity. If these patients remain pregnant after an initial course of corticosteroids, some obstetricians opt to give a rescue dose while others question its necessity. Despite multiple studies, a consensus regarding steroid duration has yet to be reached.

We aimed to assess the risk of repeated corticosteroid exposure of pregnant women at risk of preterm birth and focused on cerebral palsy as the primary outcome. We also aimed to combine current and relevant data from various studies to come up with a recommendation that can be integrated into standard practice.
METHODS

A meta-analysis of retrospective observational studies on the long term neurodevelopmental effects of repeated exposure to antenatal corticosteroids was performed.

Criteria for Considering Studies for this Review

Types of Studies

All published retrospective observational cohort studies that met the following criteria were included: (1) studies that compared the long term effects of multiple doses of prenatal corticosteroids versus placebo; (2) retrospective cohort studies that involved repeated exposure of pregnant women between 23-32 weeks age of gestation to multiple courses of prenatal corticosteroids; (3) retrospective cohort studies that followed-up exposed patients from up to early school age

Exclusion criteria were the following: (1) Articles involving animal subjects; (2) Papers using other study designs; (3) Clinical trials with different outcomes measured; (4) Clinical trials that administered only a single rescue dose; (5) Articles with no English translation; (6) studies that focused on the effects of a single dose versus multiple exposure to corticosteroids

Types of participants

Study participants were pregnant women between the ages of 23-32 weeks age of gestation who remained at risk of preterm birth despite treatment and initial administration of antenatal corticosteroids. Women were included regardless of their parity and age. Infants were followed up until early childhood age to assess for any neurologic or behavioral changes related to their exposure to repeated doses of corticosteroids.

Outcome measures

The primary outcome measured was the development of a neurocognitive impairment, specifically, cerebral palsy.

Search Methods Incorporation of Studies

A literature search for full papers and abstracts between January 2000-January 2016 using PubMed, Science Direct, MEDLINE, Cochrane CENTRAL, and HERDIN was done to determine the long term effects of repeated exposure to antenatal corticosteroids during threatened preterm labor. The keywords used were “antenatal/prenatal corticosteroids”, “glucocorticoid”, “Betamethasone”, “Dexamethasone”, “rescue”, “repeat”, “multiple” and “cerebral palsy”. Filters were activated to limit the search to retrospective observational cohort studies that were published within the last 16 years. Language restriction was limited to the English language.

Data Collection and Analysis

Selection of trials and Assessment of methodological quality

During the literature search, various abstracts were identified. Full articles were retrieved and assessed for methodological quality using the standards set by the Cochrane Handbook for Systematic Reviews of Interventions.

Data Analysis

Statistical analysis was done using the Review Manager 5 Software (RevMan5 2014). Extracted data from the three included studies were quantitative. The analysis of the primary outcome was set to a fixed effect model with a 95% confidence interval (CI). The development of cerebral palsy was categorized as dichotomous data and risk ratio (RR) under Mantel-Haenszel (M-H) was used for analysis.

RESULTS

Three retrospective observational cohort studies satisfied the inclusion criteria. Data from these trials were computed to determine the risk of developing cerebral palsy. No local trials were identified by the search.

Figure 1 shows the search scheme through which trials were included in the study. Full papers and abstracts were manually reviewed for inclusion in the study.

Figure 2 presents the data that were collected from the three included studies on the number of infants who developed cerebral palsy during the follow-up period. Asztalos et. al. (2010) (RR=0.93, 95%CI=0.53, 1.62) and Crowther et. al. (2007) (RR=0.89, 95% CI 0.51, 1.56) claim that multiple exposure to antenatal corticosteroids increase the risk of developing cerebral palsy compared to patients who were given placebo. In contrast, the study of Wapner et. al. (2007) (RR=5.76, 95% CI=0.70, 47.47) indicated that multiple exposure to antenatal corticosteroid may not increase the risk of developing cerebral palsy. This study also has a wide range of confidence interval, indicating an uncertainty in the true effect of its results.

The Forest Plot (Figure 2) shows that there is no significant difference between the two treatments. All three studies give an I2 statistic value of 31%, giving a non-significant test for heterogeneity.
DISCUSSION

Since the assembly of the NIH in 2000, the use of repeat courses of antenatal corticosteroids has been restricted to patients enrolled in randomized controlled clinical trials of sufficient power to evaluate both short-term and long-term efficacy and safety.\(^7\) These trials concluded that treatment of women at risk of preterm birth with repeat courses of antenatal corticosteroids significantly reduced the risk of neonatal respiratory distress syndrome, serious infant morbidity and severe lung disease.\(^8\) However, along with these findings, some studies also reported a mean reduction in birth weight and increase in small for gestational age infants.\(^6\)

Although there have been multiple trials on the use of antenatal corticosteroids, data is conflicting. In the multiple courses of antenatal corticosteroids for preterm birth (MACS) trial, women who were given corticosteroids every 14 days did not appreciate neonatal benefits at birth but instead noted a reduced size at birth compared with a single course.\(^9\) In a randomized controlled trial by Guinn et al., no reduction in composite neonatal morbidity was noted in weekly courses of antenatal corticosteroids compared to a single treatment.\(^10\) Statistical significance in the decreased composite neonatal morbidity was only achieved in neonates delivered at <28 weeks age of gestation.

While results on the short term effects are conflicting, long-term studies, especially on neurodevelopmental effects are scarce and limited to cohort studies.

Based on the results of the meta-analysis, the relative risk of developing cerebral palsy was higher in those exposed to multiple treatments of corticosteroids compared to those studies in which placebo is given.\(^4,5\) Another study showed an increased risk in those patients given placebo, but with a wide confidence interval, the estimated effect of its results may be uncertain.\(^6\) Overall, the three studies gave no statistically significant differences between the repeat corticosteroid group compared to the placebo (RR 1.01, 95%CI=0.69, 1.47). The computed value of I² statistic was less than 50%, indicating that the effects of the studies were reliable and not due to chance alone.

An in-depth analysis of the methodology of the studies revealed that Asztalos et al. (2010) and Wapner et al. (2007) both administered weekly courses of corticosteroids until 32 weeks or delivery, whereas, Crowther & Harding (2007) repeated the treatment every 14 days. The maximum number of treatment course that was given in all trials was 4 due to safety concerns about excessive dosing. Six infants in the repeat treatment group, born at or after 34 weeks, developed cerebral palsy cautioning the repetitive use of this treatment.\(^6\) This contradicts the study by French et al. who found that children exposed to repeated courses are protected from cerebral palsy.\(^11\)

The result of this meta-analysis is potentially reassuring. Clinicians can opt to maximize the benefits of repeated corticosteroid administration. However, long term follow-up studies are necessary to determine other outcomes as studies only included children up to two years of age.
Table 1. Included observational cohort studies

<table>
<thead>
<tr>
<th>Study and Location</th>
<th>GA at randomization, week</th>
<th>Minimal interval from first steroids to randomization</th>
<th>Intervention</th>
<th>Number of women randomized (live fetuses)</th>
<th>Mean GA at birth, week</th>
<th>Number of study treatments received= parturients</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACS-2 Asztalos et al, 2010, Canada</td>
<td>25-32</td>
<td>14-21</td>
<td>Betamethasone 24mg (divided) or placebo every 14 days until 33 weeks AOG if undelivered</td>
<td>1858 (2309)</td>
<td>33-36</td>
<td>0 = 4 1 = 351 2 = 280 3 = 139 4 = 84</td>
</tr>
<tr>
<td>Wapner et al, 2007, USA</td>
<td>23-31</td>
<td>7</td>
<td>Betamethasone 12mg or placebo every week if still undelivered by &lt;34 weeks AOG</td>
<td>495 (594)</td>
<td>34</td>
<td>4</td>
</tr>
<tr>
<td>Crowther et al, 2006 (AC-TORDS), Australia and New Zealand</td>
<td>&lt;32</td>
<td>7</td>
<td>Betamethasone 11.4mg or placebo IM every 7 days if undelivered &lt;32 weeks AOG</td>
<td>982 (1146)</td>
<td>32</td>
<td>0 = 4 1 = 185 2 or 3 = 155 ≥ 4 = 120</td>
</tr>
</tbody>
</table>

Figure 2. Meta-Analysis of risk ratio for cerebral palsy for multiple exposure to antenatal corticosteroids versus placebo using fixed effects

Figure 3. Funnel Plot for publication bias of included studies

CONCLUSION

Multiple courses of antenatal corticosteroids given weekly or every 14 days until 32 weeks of gestation does not seem to increase the risk of developing cerebral palsy compared with a single treatment. However, the studies were observational in nature and definitive conclusions about the risks of repeated corticosteroid therapies cannot be made. When steroids are used, it is still prudent to weigh the benefits against the possible complications of this treatment regimen. Additional, large scale randomized studies with long-term follow-up is necessary to determine the risks of repeated corticosteroid administration.

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Repeated antenatal corticosteroids, effects on cerebral palsy
Coconut Oil: Good or Bad for Human Health? (Asian and Philippine Perspective)

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ABSTRACT: Coconut oil is commonly used in most Asian countries such as the Philippines. However, with the introduction of the “Lipid Heart Theory”, there has been a decrease in the oil’s acceptance by consumers. This short review aims to identify the current status of coconut oil, particularly in the Philippines, in terms of its effects on human health. The health aspects considered in this review are: cardiac health, lipid profile, visceral adiposity, weight management, immunity, degenerative disease, infectious disease, skin and hair health, and oral health. Coconut oil generally confers positive effects on the health of the consumers but further studies are necessary in order to determine its long term effects.

Keywords: coconut oil, human health, lipid heart theory, Philippines, virgin coconut oil

INTRODUCTION
Coconut oil consists of 90% saturated fatty acids (SFA), 65% of which are medium chain SFA (MCFA) and approximately 30% are long chain SFA (LCFA). It is also a trans-fatty acid free oil. Various types are available in the market differing primarily in the method of oil extraction. Refined coconut oil from copra processing (e.g. dry process) is usually used for cooking while the virgin coconut oil from wet processing is used for various industries and applications.

Coconut oil is an important part of the diet and culture of several Asian countries. Moreover, it also serves as part of traditional medicine in some countries. Hence, coconut oil has widespread use throughout the world. However, its health benefits are under debate.

In 1953, Ancel Keys postulated that saturated fats can cause coronary heart disease and other health risks (known as the “Lipid Heart Theory”). This led to a shift from using coconut oil (which is composed of mainly saturated fatty acids) to other alternative vegetable oils. Since then, many studies aimed to clarify the real effect of coconut oil on the various aspects of human health. The lack of proper epidemiologic data, some possibly flawed and inconsistent in vivo studies, and shortage in clinical trials are some of the reasons why the bad reputation of coconut oil persists. Hence, this short literature review aims to identify the current status of coconut oil in terms of its health effects and to determine future research needs concerning the use of coconut oil.

METHODS
A total of 40 published articles (27 clinical trials and intervention studies; 13 review papers) from 1990 to 2016 were gathered from online research databases including PubMed, HERDIN, Science Direct and Cambridge CORE. Other search engines were also reviewed (i.e.: Google Scholar). The following keywords were used: “coconut oil”, “Asia”, “Philippines”, “virgin coconut oil”, “health”, “benefits”, “effects.” The selected studies were considered based on the following criteria: (1) the primary research subjects were Asian and (2) the effects of coconut oil or its constituents on health were discussed. Out of the 40 papers considered, 12 were published by Filipino authors primarily involving the Filipino population while 4 focused on Malaysians, representing the Southeast Asian region. India had the most number of publications considered in this review with a total of 16 papers. In brief, the selected papers discussed the effect of coconut oil or its constituents in the following aspects of health: cardiac health, lipid profile, visceral adiposity, weight management, immunity, degenerative disease, infectious disease, skin and hair health, and oral health.

Coconut Oil and Cardiac Health
Since the introduction of the Lipid Heart Theory, many researches using animal models and several clinical trials were conducted worldwide using coconut oil. There were opposing views as to the oil’s effect on the circulatory system particularly on the lipid profile of consumers as well as the risk of developing heart ailments. In the Asian population, several studies indicated that coconut oil consumption can be good for the heart and is not involved in the
development of atherosclerosis and coronary heart disease.\textsuperscript{2,3,6,7,8,9}

To support the claim that coconut oil is good for the heart, several clinical trials were conducted to determine the lipid profiles of certain populations consuming coconut oil as part of their diet. For instance, two studies found out that a decrease in the level of Low Density Lipoprotein (“bad” cholesterol) in the serum of healthy Asians was achieved by the experimental group which consumed MCFA from coconut oil as part of a standardized diet.\textsuperscript{10,11} This result was corroborated by the review of Hedge.\textsuperscript{12} Moreover, consumption of coconut oil increased the level of High Density Lipoprotein (“good” cholesterol) in pre-menopausal Filipino population.\textsuperscript{13} However, the diet used in this study was not controlled and the consumption of coconut oil was based on recall. Meanwhile, coconut oil seemed to have no effect on lipid-related cardiovascular risk (Lipoprotein A levels, non-esterified fatty acid levels, etc.) of coronary heart disease patients.\textsuperscript{14} Since majority of the saturated fatty acids present in coconut oil is of medium-chain type (which is believed to be metabolized easily), it is not primarily involved in the synthesis and build-up of cholesterol levels in the blood serum.\textsuperscript{1} Meanwhile, a study on the plaque composition of 71 coronary artery bypass patients consuming coconut oil found that the amount of lauric acid (which is the most abundant fatty acid in coconut oil) in the atheromatous plaque of the patients is significantly lower compared to the other fatty acids.\textsuperscript{15} This could indicate that serum fatty acids derived from oil consumption is not the sole basis for concluding that a certain diet may induce plaque formation.

Studies on the effect of consuming Virgin Coconut Oil (VCO) revealed an almost neutral effect on lipid profile of human subjects. For instance, Liau, \textit{et. al.} indicated that there is a non-significant change in the total cholesterol and lipoprotein (both HDL and LDL) levels of all seven male subjects consuming 30mL/ day of VCO for four weeks.\textsuperscript{16} Meanwhile, females (13) seem to be unaffected. However, this study only tested a small population size and retained an uncontrolled dietary regime which may have significant effect on the observed results. In another study, significant decrease on mean HDL, albeit minimal in amount, and no changes in total cholesterol, triglycerides and LDL were also observed for 30 Filipino subjects.\textsuperscript{17} The observations may indicate that VCO may have a positive effect on the lipid levels in the blood. However, the relationship of gender must still be clarified. Furthermore, these findings suggest that the different types of coconut oil can have varying effects on the lipid profiles of the Asian consumers. This aspect can also be of potential research significance.

Epidemiological data on the effects of coconut oil on the cardiac health of long-term consumers is available. Kumar and Sabitha, \textit{et. al.} found that habitual or routine consumption of coconut oil (in moderate amounts), along with healthy diet, has no specific role in the risk and development of coronary heart disease in Kerala population in India.\textsuperscript{8,9} This population is known to consume coconut oil as part of their normal diet. Similarly, a review on the Sri Lankan consumption of coconut oil indicated that the risk of developing coronary heart disease is significantly lower in the rural areas of Sri Lanka where high consumption of coconut oil is evident.\textsuperscript{1} Data from the Philippine National Nutrition Survey of 2003 revealed a low incidence of heart disease in Bicol Region where consumption of coconut oil is highest. This was indirectly corroborated by the low mortality rate in Bicol Region in terms of heart ailments.\textsuperscript{2,18} Based on this data, it appears that long term use of coconut oil may have a positive effect on cardiac health.

**Coconut Oil, Weight Management and Nutrition**

Coconut oil is primarily composed of saturated fat. Hence, it is widely believed to accumulate as body fat leading to obesity, and consequently, heart ailments. However, majority of the saturated fat component of coconut oil is in the form of MCFA which is believed to be easily metabolized. MCFA can be directly absorbed from the intestinal tract and can be rapidly metabolized by the liver to provide usable energy.\textsuperscript{1} Among Asians, majority of the studies and reviews indicated good effects of coconut oil in controlling weight,\textsuperscript{12,19} visceral adiposity\textsuperscript{10,16,20} and even nutrient absorption.\textsuperscript{3,21}

A study found that transcutaneous feeding of coconut oil in 25 preterm newborns resulted in weight gain of the experimental group over a period of seven days.\textsuperscript{19} This supports the idea that MCFA from coconut oil can be an efficient cellular food. However, the mechanism of this transcutaneous feeding was not discussed in the paper. Meanwhile, Hedge indicated that coconut oil, being a low calorie fat, can also be used to control body weight. This is supported by several studies that measured the effect of coconut oil consumption in the formation of visceral adiposity and fat deposition.\textsuperscript{12} Liau, \textit{et. al.} found out that the male subjects in their study significantly reduced abdominal fat and waist circumference after consumption of VCO for four weeks.\textsuperscript{16} Similarly, Aoyama, \textit{et. al.} found out that MCFA consumption (from coconut oil) helps suppress the accumu-
ulation of body fat and consequently reduce visceral adiposity, waist size and hip size in Japanese subjects with high Body Mass Index (BMI). Similar results were reported among healthy subjects after consumption of MCFA for 12 weeks. However, some studies with contradictory results also exist. For example, Abella, et al. found that VCO does not induce a statistically significant reduction in body fat and weight of obese and overweight Filipinos after 6 weeks of oil consumption on a 45mL/day basis. However, only 12 patients were included in this study so the results may have been an underestimation of the actual effect. Several side effects were noted among study subjects assigned to high consumption of coconut oil including gastrointestinal irritation, diarrhea, flatulence and prostration. Based on current data, it appears that further study is needed to determine the effect and safety of consuming coconut oil as a weight control supplement.

Amarasiri & Dissanayake indicated in their review that coconut oil may aid in absorption of minerals (Calcium and Magnesium) in the intestine. Furthermore, Aoyama, et al. stated that diet rich in MCFA can be useful in the treatment of disorders in lipid metabolism particularly for the population with relatively high BMI. Fortification of coconut oil with Vitamin A was also found out to help with the reduction of Vitamin A deficiency in Filipino children as compared to Vitamin A supplement alone. Meanwhile, coconut oil has a neutral effect on feeding intolerance and possibly in necrotizing enterocolitis in infants because of its minimal effect in the osmolality of breast milk. It may therefore be favorable to consume coconut oil, in moderation, to help in the proper digestion and nutrient absorption of healthy adults but not among infants.

**Coconut Oil, Immune System and Cure for Diseases**

Many properties of coconut oil can be attributed to its high amount of MCFA. These MCFA have positive effects on the overall well being of human and animal subjects particularly in enhancing the functions of immune system and fighting disease-causing agents. In some parts of Asia, coconut oil is used in conjunction with other herbal products as traditional cure for various ailments.

Numerous studies and reviews assessed the bioactivity of coconut oil against common pathogens. Broad spectrum antibacterial, antifungal and antiparasitic activity were reported in both animal and human subjects. In contrast, a study by Hlady, et al. found that the risk of neonatal tetanus can be increased when coconut oil is applied in the vagina of pregnant women—a common practice in Pakistan. However, this observation is not due to the inherent property of coconut oil but rather due to the possibility of contamination of coconut oil with bacterial pathogens.

A particularly interesting property of coconut oil is its potent antiviral activity. Coconut oil can be very effective against enveloped viruses such as Influenza virus and Hepatitis C virus due to its inherent hydrophobicity and the presence of monolaurin. A pilot clinical trial by Dayrit supported antiviral activity of coconut oil with the observed reduction of viral load in 15 Filipino HIV patients. It is therefore necessary to conduct more clinical research to confirm (or refute) this interesting property.

Various review studies provide evidence that coconut oil can enhance the immune function. In particular, increase in cytotoxic and helper T-cells were reported with the consumption of VCO supplemented with Zinc. However, the mechanism of VCO inducing this effect was not discussed in these reviews. In another review, virgin coconut oil inhibited the effects of chronic inflammation by reducing granuloma formation and alkaline phosphatase activity in the blood serum. Meanwhile, blood thrombogenicity was found to be promoted in subjects consuming coconut oil by lowering tissue plasminogen activator antigen concentration and increasing the platelet count. This finding indicates faster healing and recovery after an injury. However, contradictory results were presented by Voon, et al. stating that coconut oil diet does not alter the level of thrombogenicity indices in the blood of Malaysian adults in a controlled diet. This property needs to be clarified in future researches.

Antioxidant activity of coconut oil was also evaluated in several studies. Promising results in increasing antioxidant levels due to the presence of polyphenols, tocopherol, tocotrienol, phytosterol, phytostanol and flavonoids in coconut oil have been reported. Coconut oil, particularly VCO, is less affected by oxidation as evident by its low total oxidation (TOTOX) value after five days of use. It is therefore less prone to free radical formation (hence greater oxidative stability) even after re-use. This finding is significant since oil re-use is an inevitable practice in several Asian countries.

A review by Neema Johnson, et al. revealed the potential of coconut oil in treating Alzheimer’s disease. According to this review, the ketones and ketoacids produced by the metabolism of MCFA from coconut oil can serve as an alternative neuron fuel that prevents the degeneration of nerve cells. However, formal clinical studies are needed to prove this notion since the data provided by the review is...
Coconut Oil and the Skin, Hair and Oral Health

Coconut oil is traditionally used in some parts of Asia as an emollient and skin moisturizer. Various studies tried to compare the effects of using coconut oil versus mineral oils in improving skin quality and treating skin diseases. Results of these studies are promising. For instance, a study by Dikhil et al. found that the use of coconut oil as back emollient for chronic bedridden patients in North India can significantly reduce the risk of developing pressure ulcer. Meanwhile, Evangelista, et. al. found out that VCO can address the inflammation caused by Atopic Dermatitis and may also prevent bacterial infection of the skin in Filipino patients inflicted with Pediatric Atopic Dermatitis. This was also supported by several studies that showed that VCO has components naturally known to confer antisepthic properties to the skin while maintaining epidermal integrity. They also found out that VCO lowers the risk of developing pruritus, erythema, dermatitis and neonatal bloodstream infections, and is well tolerated by the users. Hence, coconut oil remains to be a safe and effective alternative to mineral oils in terms of moisturizing the skin and preventing damages.

Only few studies have evaluated the efficacy of coconut oil for hair treatment. It is widely accepted that coconut oil can confer good physical characteristics to the hair in terms of smell, luster, and strength. In the study comparing different oils, Sesa oil was found out to be more effective as compared to VCO in terms of its outcomes in treating hair ailments. In fact, only about 17% of the subjects got “good” or “excellent” scores regarding the effect of VCO on their hair. Swishing of coconut oil in the oral cavity (known as Kavalgra Graha or Gandoosha) is considered a part of tradition in India. In the study of Peedikayil, et. al., they found that coconut oil can help decrease the occurrence of plaque-related gingivitis by up to 50%. Lauric acid, a constituent of coconut oil, can react with the alkaline components of the saliva to form soap-like compounds that aids in the cleansing of teeth and removal of plaques.

CONCLUSION

In summary, coconut oil appears to be beneficial in terms of nutrient absorption, treatment against common infections, immune function, skin health and oral health. Although majority of the studies point out the good effects of coconut oil in terms of cardiac health, weight management, hair care and even in treatment of viral infection and degenerative diseases, controlled clinical studies are needed to confirm its efficacy. Clinicians and scientists, particularly in Asia and Philippines, are encouraged to conduct clinical studies using coconut oil in these areas of human health.

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